

53. (New) The process of claim 47,  
wherein the dissolving step comprises refluxing the organic solvent;  
wherein the adding step comprises adding water dropwise to the solution;  
wherein the precipitating step comprises cooling the solution to about 10 °C; and  
wherein the drying conditions comprise heating the precipitated mirtazapine to the reflux temperature of the organic solvent under reduced pressure.

### **REMARKS**

Applicants would like to thank the Examiner for extending Applicants the courtesy of an interview on June 11, 2002. Claims 29-45 are currently pending in the application. Entry of the foregoing amendments is respectfully requested. Upon entry of the amendments, claims 30-35, 37-41, and 46-53 will be pending.

#### **I. Rejections under §§ 102 and 103(a) over Van der Burg or Nickolson**

The Examiner has rejected claims 44 and 45 under 35 U.S.C. § 102(b) as anticipated by Van der Burg or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Van der Burg. The Examiner has also rejected these claims under § 102(e) as being anticipated by Nickolson. Applicants respectfully disagree for at least those reasons of record. Nonetheless, to expedite prosecution, Applicants have obviated these rejections by canceling these claims.

#### **II. Rejections under § 102(b) over Kaspersen**

The Examiner has rejected claims 29-43 under 35 U.S.C. § 102(b) as being unpatentable over Kaspersen et al. The Examiner acknowledges that Kaspersen does not disclose adducts of mirtazapine and water. Rather, the Examiner asserts that the products disclosed in Kaspersen are “presumed” to be the claimed adduct (i.e., inherently formed) because Kaspersen's crystallization process “appears to be the same” as Applicants'. Applicants respectfully traverse.

“To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by

probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” MPEP §2112.

Kaspersen discloses “crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colorless crystals . . . .” Kaspersen does not dry the resulting crystals. In contrast, the claimed crystalline adduct of mirtazapine and water is made by a different process, resulting in a different crystalline structure. The claimed crystalline adduct is preferably prepared by crystallizing mirtazapine from a solution of alcohol and water, recovering the crystallized mirtazapine, and drying the crystallized mirtazapine, preferably at an elevated temperature and under reduced pressure.

Moreover, Kaspersen's mirtazapine is clearly different from the claimed adduct of mirtazapine and water, which contains up to about 3% by weight water, because Kaspersen's mirtazapine and the claimed adduct have different properties. In the pending Office Action, the Examiner stated that Applicants can overcome the rejection by showing that their product is different from that obtained by Kaspersen. During the June 11 interview, the Examiner also stated that a Rule 132 declaration that helps overcome the rejections would be considered. As shown in the attached Aronhime Declaration (Appendix A), for adducts containing 0.2 - 3.2% water, which were made in accordance with the specification (see Example 6), a white to creamy powder was obtained with a melting point of about 116 °C and with IR peaks at about 1587/1566/1467/1444 cm<sup>-1</sup>. In contrast, Kaspersen's mirtazapine was observed to be colorless crystals having a melting point of about 124-126 °C and with different IR peaks at 1460 and 1440 cm<sup>-1</sup>. Accordingly, Kaspersen's mirtazapine form clearly does not fall within the scope of the claimed adduct of mirtazapine and water and, thus, cannot anticipate the claims. Applicants therefore respectfully request that this rejection be withdrawn.

### III. Rejections under § 112, Second Paragraph

The Examiner has rejected claims 36 and 42 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner states that claims 36 and 42 appear to be duplicates of claim 30. Applicants respectfully disagree for at least the reasons of record. However, to expedite prosecution, Applicants have obviated the rejection by canceling claims 36 and 42.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request allowance of the pending claims. The Examiner is invited to contact the undersigned attorney regarding any matter concerning the pending application.

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Respectfully submitted,



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**MARKED-UP VERSION OF AMENDED CLAIMS**

30. [The] A crystalline adduct of mirtazapine and water [of claim 29] containing up to about three weight percent water.
31. [An] The adduct of mirtazapine and water of claim 30 prepared by precipitation from a solvent comprising water and either an alcohol or acetone.
37. A[n] crystallized adduct of mirtazapine and water prepared by:
1. slow addition of water at elevated temperature to a mixture of mirtazapine and an organic solvent selected from the group consisting of alcohols and acetone,
  2. precipitating the adduct by cooling, and
  3. separating the adduct from the water and organic solvent.]
- i) crystallizing mirtazapine from a solution comprising water;
- ii) recovering crystallized mirtazapine; and
- iii) drying the crystallized mirtazapine until the crystallized mirtazapine contains up to about 3 percent water.
38. The adduct of mirtazapine and water of claim 37 wherein the [organic solvent is] solution also comprises an alcohol.
41. The adduct of mirtazapine and water of claim 40 wherein [from about one to about four volumes of water are added relative to the amount of ethanol] the solution comprises a ratio of ethanol:water ranging from about 1:1 to about 1:4.